THIOCYANATE THERAPY*

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DURING the past twenty years, over three score papers have been published on various aspects of thiocyanate therapy—its efficacy, or otherwise, and its possible toxic effects. Only three of these[1, 3] have discussed the selection of patients for therapy, while none have approached a systematic method of administration. This paper reports our experience with this drug, special attention being paid to these two aspects.

Administration.—Until Barker[4] showed that the concentration of the thiocyanate radicle in the serum could be determined by a simple chemical procedure, this drug had been given more or less by rule of thumb. With no safe guide to dosage, many toxic reactions naturally occurred, and one finds nine fatal poisonings reported in the literature prior to 1936. With the introduction of the photoelectric colorimeter, it has become a simple procedure to check serum levels regularly, and to maintain an optimum concentration. This has been stated by Barker, and confirmed by the experience of others as well as ourselves, to be between 8 and 14 mgm. % of the SCN radicle.

Obviously, when a decision has been made to assess the effect of this drug in a given patient, the therapeutic goal is to administer the drug in a cumulative fashion so as to achieve the desired serum level as smoothly, quickly and accurately as possible and thereafter to determine the "maintenance dose" which will maintain this level, without dangerous cumulation.

We decided to see if a system of "loading" could be devised, similar to that utilized with rapid digitalization methods, so that the therapeutic level would be arrived at in a matter of hours rather than of days, treatment thereby being rendered more efficient, with the stay of the patient in hospital materially shortened.

Our first problem was to calculate the dosages required. Earlier, it had been shown by Lavietes *et al.*[5] that the thiocyanate radicle was evenly distributed in the extracellular fluid of the body. This is usually considered to represent, depending on body weight and constitution, between 15 and 20% of the total body weight, although Page[6] states that it may be as much as 30%. A formula for calculating dosage has been suggested by Blaney, Geiger and Ernst,[7] as follows:

1. Weight of the patient x 0.2 = volume of extracellular fluid through which thiocyanate is to be distributed.
2. Volume of E.C.F. in kgm. x 10 x desired conc. of SCN (stated in mgm. %) = desired total dose of SCN in mgm.
3. SCN dose x $\frac{97}{58}$ = total dosage of potassium thiocyanate (in mgm.).

1 and 2 may be combined, thus:

$$\frac{\text{Weight of patient (in lb.) x 0.2 x 10 x desired level (in mgm.)}}{2.2}$$

and condensed to: weight of patient in lb. x 0.9 (constant) x desired level (in mgm) = mgm. of KSCN required to "cyanate" the patient.

We decided to use this formula to calculate the amount of the drug needed to establish desirable serum levels, and developed two oral methods of "loading": (*a*) massive—giving the patient, the total "loading dose" in three equal amounts, within a period of 24 hours; (*b*) spaced-spreading approximately the same total dose over a period of three days, two doses being given each day. These decisions were purely arbitrary.*

Subject material and procedure.—The subject material of our study comprises 140 persons: 50 out-patients from the Hypertension Clinic, and 30 in-patients from the Kingston General Hospital, 10 healthy interns and 50 under-graduate medical students from Queen's University.

The observations were carried out for varying periods. The students and interns, on whom the loading, maintenance and excretion studies were largely performed, were followed for from one to three weeks. The group of patients under therapy for hypertension have been studied in some cases for as long as 18 to 36 months. The majority have been followed for less than a year.

Chemical estimation of serum potassium thiocyanate was performed as follows: To 1 ml. serum is added

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4 ml. distilled water and 5 ml. trichloracetic acid. After agitation, the mixture stands for 10 minutes and is then filtered. To 5 ml. of filtrate is added 1 ml. of ferric nitrate reagent. This solution is then shaken and read in a Leitz photo-electric colorimeter, using filter of wavelength 440 mμ. The readings are compared with a calibrated scale prepared from standardized amounts of known thiocyanate radicle.

Loading experiment.—Our first loading experiment with the drug was undertaken with four chronically ill but ambulatory patients. We attempted to bring these cautiously to a low serum level of 8 mgm. % by administration of the entire calculated amount in a single dose. The concentrations obtained were much lower than expected (35 to 70% of the calculated level). We felt that abnormal water balance might be a factor here, and hence included a group of healthy interns in our subjects for loading experiments. Levels were still quite low, and it became apparent that the degree (and incompleteness) of intestinal absorption was an important factor in our discordant results. To overcome this factor, and to establish, if possible, the validity of our formula, it was decided to administer the drug intravenously, using a 5% aqueous solution of sodium thiocyanate of our own preparation, dosed according to the above formula. (The sodium salt was selected because it is the predominant ion of extracellular fluid and because potassium salts cause considerable irritation of the vein wall, leading to sclerosis.)

Six loading experiments, with an attempted result of 5 mgm. %, were carried out, blood samples being taken 2 and 4 hours after parenteral administration of the drug. The highest levels obtained were 3.2 mgm. %, or about 66% of that desired. The formula was then arbitrarily revised, thus, 5/3.2 x 0.9 (the former constant) which gave us a new constant of 1.4.

TABLE I.

URINARY EXCRETION OF KSCN

Subject		*B.B.*			*A.M.*			*J.W.*	
Day	*Volume (c.c.)*	*Concentration of KSCN (mgm. %)*	*Excretion of KSCN (mgm.)*	*Volume (c.c.)*	*Concentration of KSCN (mgm. %)*	*Excretion of KSCN (mgm.)*	*Volume (c.c.)*	*Concentration of KSCN (mgm. %)*	*Excretion of KSCN (mgm.)*
1	1480	14.8	219.0	1350	18.7	252.5	980	18.7	183.3
2	2050	14.1	289.1	1600	16.7	267.2	900	17.1	153.9
3	1050	17.8	186.9	1230	16.0	196.8	620	19.7	122.1
4	1970	19.3	380.2	1540	21.4	329.6	1190	17.8	211.8
5	1040	16.7	173.7	1290	24.8	318.9	1110	20.7	229.8
6	1530	27.5	410.9	1190	22.1	263.0	940	14.8	129.1
7	1680	27.2	456.9	1350	16.7	222.5	830	17.1	141.9
Total excreted			2116.7			1850.5			1171.9
Total ingested			2800.0			2800.0			2800.0
Recovery			75.6%			66.1%			41.8%

*It is noted that some of the drug unaccounted for is explained by the changed concentration of the extracellular fluid of the subjects For example, B.B.'s serum level rose from 3.3 to 10.5 mgm. %. Using a 20% fraction of body weight as the extracellular compartment, this would explain the presence of $\frac{20}{100}$ x 135 x 7.2 or 194.4 mgm., almost 7% of the amount ingested. On the other hand, the serum levels of A.M. and J.W. decreased. Other avenues of excretion not established quantitatively were fæces and perspiration.

TABLE II.

URINARY EXCRETION OF NaSCN, 5%

Subject		*A.M.*			*J.W.*			*D.W.*	
Day	*Volume (c.c.)*	*Concentration of NaSCN (mgm. %)*	*Excretion of NaSCN (mgm. %)*	*Volume (c.c.)*	*Concentration of NaSCN (mgm. %)*	*Excretion of NaSCN (mgm. %)*	*Volume (c.c.)*	*Concentration of NaSCN (mgm. %)*	*Excretion of NaSCN (mgm. %)*
1	1230	33.8	415.7	1250	17.6	210.0	1330	14.0	189.6
2	1210	32.8	396.9	660	19.4	128.0	1860	10.5	195.3
3	1210	18.2	220.2	1520	11.5	174.8	1520	10.3	156.6
4	860	10.9	93.7	760	14.4	109.4	490	11.5	56.4
5	1290	7.0	90.3	940	10.9	102.5	620	10.9	67.6
6	690	7.0	48.3	950	7.8	76.1	1840	6.3	115.9
7	920	6.3	57.9	990	7.8	77.2	1000	6.3	63.0
8	1660	4.3	71.4	550	8.9	49.0	1250	5.9	73.6
9	1850	3.9	72.2	1330	6.7	89.1	1450	4.3	62.4
10	850	4.8	40.8	930	5.9	54.9	1160	5.9	68.4
11	1530	3.4	52.0	980	4.3	42.1	1220	4.3	52.5
12	1430	3.4	48.6	....	....	.....	....	....	.....
Total excreted			1608.0			1114.1			1101.3
Total injected			1580.0			1440.0			1340.0
Recovery			100.0% +			77.0%			82.0%

Using this constant in our formula, we attempted a final concentration of 8 mgm. % in three subjects and obtained end-points of 7.6, 7.6 and 7.8 mgm. %—an average of 96% of the desired level, and well within the range of our experimental error.

Excretion of KSCN.—Studies were next carried out on the excretion of the drug. It was proposed to measure the thiocyanate radicle in the urine and fæces of subjects receiving this material. Demonstration of urinary thiocyanate was very simple; its presence in the fæces could never be proved. Simple recovery experiments from aliquots of stool, (from which the bile salts had been absorbed by Fuller's earth) proved the insensitivity of our photoelectric method and the impracticability of the procedure.

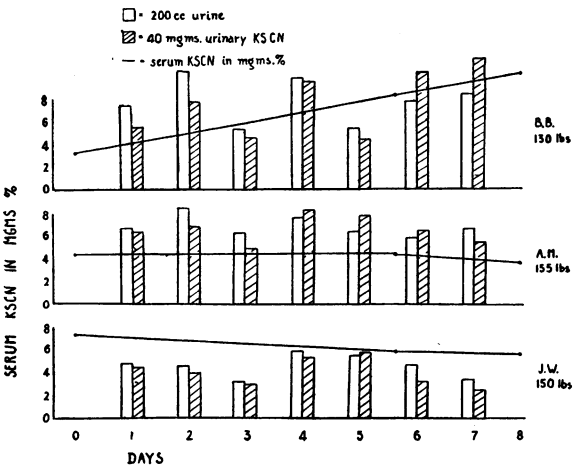

Chart 1.—Loading and excretion study using KSCN orally.

We were the more ready to abandon this research, and also an investigation of a third avenue of possible excretion — perspiration— because our urinary studies unexpectedly revealed that some individuals, at least, eliminate thiocyanate completely in their urine. Thirteen subjects were loaded, a few by mouth, most parenterally, and 24-hour urine collections were made and studied for periods up to 11 days following. Of the three subjects to whom the drug was orally administered, a recovery* averaging 61% (range 42 to 75%) was obtained. The average recovery from 8 subjects "cyanated" intravenously was 83% range 63 to 100% (2 cases). Two subjects loaded by both routes showed larger recoveries from the intravenous dosing (82 and 77% respectively as against 66 and 42% respectively from oral administration). (See Tables I and II and Charts 1 and 2.) We felt this sufficient grounds for postulating indifferent intestinal absorption as the major factor governing the end results following oral administration of the drug.

Further modification of formula.—For practical considerations, we felt that it was inadvisable to utilize the intravenous route when using the thiocyanates therapeutically. Despite

* Error in the colorimetric estimation of urinary thiocyanate was avoided by using an untreated specimen as a blank against which the colorimeter was standardized.

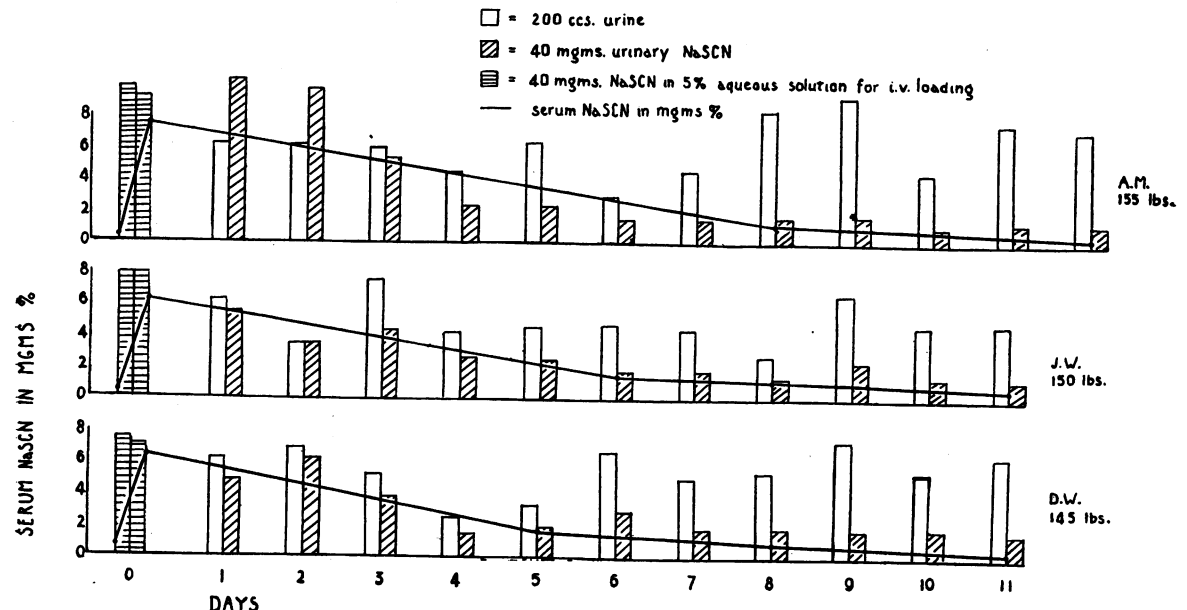

Chart 2.—Loading and excretion study using NaSCN intravenously.

the incompleteness and variability of intestinal absorption when the selected preparation of potassium thiocyanate was given orally, we attempted to devise a formula which would help us determine a loading procedure, which would be safe and applicable under widely varying conditions. Returning to our previous formula, we raised the constant from 1.4 to 1.7 (to allow for the increased atomic weight of the potassium salt used in the enseals). Assuming an average weight of 150 lb. and a desired serum concentration of 10 mgm. %, there would be required, for massive loading (allowing 100% absorption and no excretion of the drug during the loading procedure), 150 x 1.7 x 10 or 2,550 mgm., that is, between twelve and thirteen 200 mgm. enseals.

TABLE III.

LOADING LEVELS OF GROUP 1—24 HOUR METHOD

		— Serum KSCN in mgm. % —			
		Basal	*24 hours*	*7 days*	*14 days*
Subject	*Weight lb.*	*mgm. %*	*mgm. %*	*mgm. %*	*mgm. %*
1	145	0.3	9.8	8.0	9.4
2	155	1.3	8.5	11.2	11.2
3	145	0.3	9.0	7.7	7.4
4	145	0.9	9.0	8.5	8.5
5	190	0.5	6.5	5.2	5.2
6	140	1.0	10.5	8.0	8.0
7	150	0.7	9.8	8.5	9.4
8	145	0.7	8.5	4.3	4.3
9	185	1.3	8.5	5.7	4.7
10	175	1.8	8.0	7.0	5.0
11	135	1.3	9.0	9.8	14.8
12	150	0.3	9.4	8.0	5.0
13	180	0.7	8.5	8.0	6.0
14	130	1.3	9.0	2.7	3.8
15	130	1.0	6.8	7.2	7.0
16	126	0.3	7.0	12.2	9.0
17	160	1.0	8.0	5.7	4.3
18	127	1.0	12.2	11.5	10.5
19	150	0.3	9.0	9.8	8.0
20	145	1.0	7.0	8.5	4.4
21	115	0.9	12.5	14.5	14.8
22	175	0.3	6.5	6.8	4.4
23	165	1.0	9.0	9.8	9.4
24	150	0.7	8.5	8.5	11.2
25	148	0.9	7.0	5.5	4.3
Total		19.9	221.5	202.6	189.7
Average		0.8	8.9	8.1	7.6

This new formula was now tested by adopting two loading procedures and taking initial thiocyanate blood levels. The first procedure consisted of the administration of 12 tablets in 12 hours (3 doses of 4 tablets each) and the determination of the thiocyanate level at the end of 24 hours. The second procedure consisted of the administration of 13 enseals in six divided doses over a 60-hour period, with the thiocyanate level being determined at the end of 72 hours. The first procedure was tested on 25 medical students and the second on 22. In each case, subjects were maintained, after the initial loading, on an empirically determined "maintenance" dose of 400 mgm. or two 200 mgm. enseals daily. Tables III and IV summarize the results of these trials.

The most notable feature of these tables is the scatter distribution of the serum levels obtained; there is no dominant trend in the group picture. The desired end-result had been 10 mgm. %. The 24-hour loading average approximated this most closely—being 8.9 mgm. at the end of 24 hours, 8.1 mgm. on the 7th day and 7.6 mgm. on the 14th day (see Chart 3). That is, there was considerable constancy in the average levels, with a fall of only 1.3 mgm. over a two week period. Further, the apparent heterogeneity of the thiocyanate curves was shown on analysis to be due to the variation in the subjects' weights. Thus, 13 subjects with weights below 150 lb. (average 136 lb.) had serum levels rising higher than the median for the group (9.8, 8.3 and 8.1 mgm. % respectively). The twelve students with weights over 150 lb. (average 165 lb.) had serum concentrations slightly lower than the group medians (8.3, 7.9 and 7.0 mgm. % respectively).

TABLE IV.

LOADING LEVELS OF GROUP 2—3 DAY METHOD

		— Serum KSCN in mgm. % —			
		Basal	*72 hours*	*7 days*	*14 days*
Subject	*Weight lb.*	*mgm. %*	*mgm. %*	*mgm. %*	*mgm. %*
1	120	1.0	9.8	9.8	10.5
2	145	1.0	8.5	9.0	9.8
3	110	1.0	9.4	8.0	7.0
4	130	0.7	8.5	10.5	11.2
5	138	0.7	9.4	9.8	15.4
6	156	1.3	8.5	6.5	7.4
7	175	2.7	7.4	3.3	3.3
8	180	0.7	3.8	5.2	4.3
9	160	1.0	5.7	7.0	8.0
10	145	0.7	5.7	5.2	3.8
11	150	1.3	8.0	9.8	8.2
12	145	0.7	4.3	8.0	9.8
13	210	1.0	6.0	5.2	7.4
14	170	1.0	5.2	7.0	9.4
15	137	1.3	5.2	7.4	5.0
16	145	0.3	7.0	9.0	11.5
17	165	1.0	6.8	8.0	8.0
18	150	0.3	6.0	7.2	7.4
19	148	1.0	7.0	9.4	11.2
20	145	0.3	3.8	6.0	5.7
21	148	1.1	7.0	8.0	8.5
22	130	0.7	8.5	9.6	8.0
Total		20.8	151.15	168.9	180.8
Average		0.9	6.9	7.7	8.2

The 72-hour loading method shows the same absence of a predominating pattern. The average serum concentrations after 3, 7 and 14 days,

were 6.9, 7.7 and 8.2 mgm. % (see Chart 4). The curve joining these points rises constantly over the 11-day period by an amount (1.3 mgm. %) similar to the decline of the line joining the medians of group 1. As in group 1, the irregularity of the plotted serum values is related to the weight variation of the subjects.

DISCUSSION

While the initial level after loading by this method averaged 2 mgm. % less than by the 24-hour method, the levels obtained are, for clinical purposes, not significantly different. With both procedures, the patient is carried to the lower level of the therapeutic range (8 to 14 mgm. %), which is all that should be attempted safely with any patient who is being "cyanated" for the first time. In the first group, about one-half the patients approximated the desired 10 mgm. % figure. In the remainder, it was felt that variations in weight, body build, extracellular fluid and, most importantly, the degree of intestinal absorption of the drug, accounted for any discrepancies noted.

An obvious reason for the failure of more patients in the second group to attain the desired end-point was the actually smaller loading dose. These patients were provided with only one extra 200 mgm. enseal to balance their excretion of the drug over a 72-hour loading period when, as it was later realized from studies on the maintenance dose, five tablets would have been a fairer allowance.

If we now inspect the maintenance levels of group 1, following the initial loading period, from the viewpoint of range rather than of averages (See Table 3), it will be seen that the levels after 24 hours ranged from 6.5 to 12.5 mgm. %, after 7 days from 2.7 to 14.5 mgm. % and after 14 days from 4.3 to 14.8 mgm. %. Two subjects only, Nos. 11 and 21, developed dangerously high concentrations. No. 21, a 115 lb. female, had an initial loading concentration of 12.5 mgm. % and her level rose steadily thereafter. By contrast, No. 18, a 127 lb. female, had nearly the same initial loading level, 12.2 mgm. % but her level subsequently declined progressively. On the other hand, No. 11, a 135 lb. male, had a concentration of 9.0 mgm. % at the end of 24 hours, maintained approximately the same level during the next week, but showed a rise of 5.8 mgm. % to 14.8 mgm. % during the second week. These examples emphasize the individual variability of absorption and excretion.

A similar analysis of the range of serum concentrations in group 2 (see Table IV) shows serum values after 72 hours ranging from 3.8 to 9.8 mgm. %, after 7 days from 3.3 to 10.5 mgm. % and after 14 days from 3.3 to 15.4 mgm. %. With the exception of the last named, No. 5, a 138 lb. male, all concentrations may be considered safe.

It is evident from these results that, using an arbitrary maintenance dose of 400 mgm. or 6 grains daily, the thiocyanate levels were some-

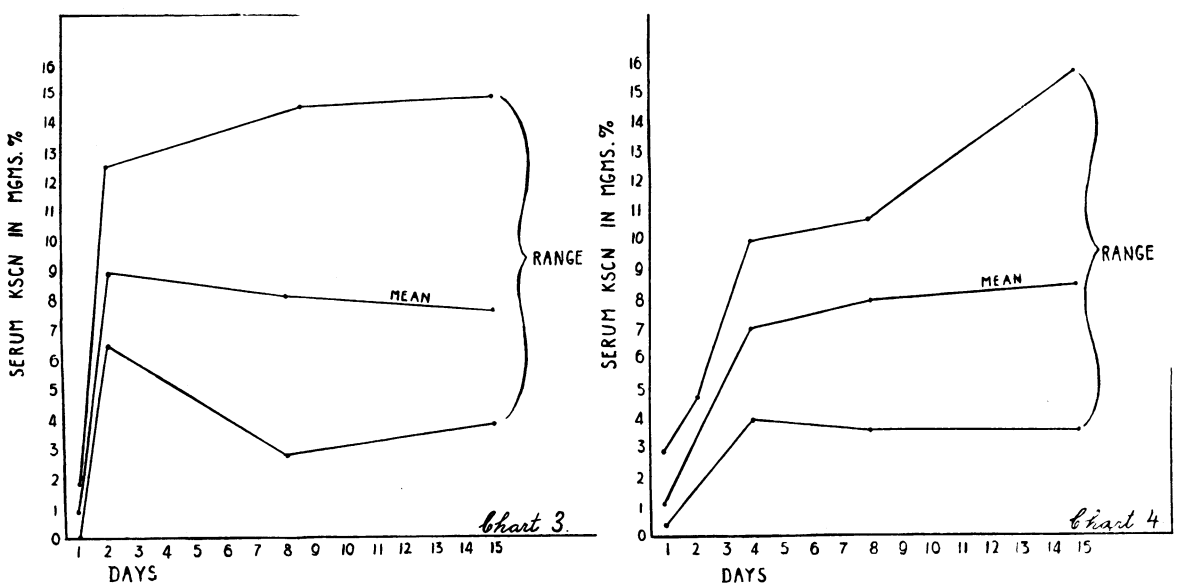

Chart 3.—24-hour loading and maintenance study using KSCN orally.
Chart 4.—72-hour loading and maintenance study using KSCN orally.

what more stable in the second group loaded over a 72-hour period. In actual clinical practice, however, the first method of 24-hour loading is greatly to be preferred and one of us (W.F.C.) has used this method over a three-year period in his hospital practice and has found it to be safe and satisfactory. The procedure at present adopted is as follows:

An arbitrary loading dose is selected, averaging 12 x 200 mgm. enseals of potassium thiocyanate. This dose is reduced in the case of very small adults to 10 enseals, and increased in the case of very large adults to 14 enseals. These are now given in 3 doses at 4-hourly intervals (originally 6-hourly). The following morning, 24 hours or less after the first dose, a serum thiocyanate estimation is done, and 2 enseals are given; one in the morning and one in the evening. This procedure is repeated daily thereafter, but if the initial level of thiocyanate is within the therapeutic range, and the daily levels thereafter continue to rise, the maintenance dose is adjusted appropriately downwards. Conversely, of course, a larger daily dose may be administered to those patients whose level, after 24 hours, is below the therapeutic range. It is exceptional to find a level of less than 6 mgm. % after the loading dose. A number of patients have been found, however, whose daily requirement, to maintain a therapeutic level, approximates 3 enseals, or 600 mgm. It should be emphasized that, not only does the maintenance dose vary widely from patient to patient, but it may vary considerably in the *same* patient from time to time.

After a decision to try thiocyanate has been made, we have usually found it possible, with the above method, to achieve therapeutic blood levels within a 24-hour period, and to observe the effects of such levels on the patient's symptoms and blood pressure thereafter over a period of 4 or 5 days. At the end of this time, it has usually been possible to decide whether a continuation of the therapy is worthwhile, and also to arrive at a fairly accurate idea of the daily maintenance dose required to maintain the desired serum concentration of the drug. After discharge from hospital, arrangements are always made for a careful follow-up, either by the family physician or in our out-patient clinic. For some weeks, the serum level of thiocyanate

TABLE V.

TOXIC REACTIONS DURING EXPERIMENTAL ADMINISTRATION OF POTASSIUM THIOCYANATE ENSEALS

	Initials	*Reactions*	*Serum KSCN level*
1.	W.W.	Severe headache (subject experienced slight malaise before starting experiment).	November 1, 1945, 1.3 mgm. % November 2, 1945, 9.4 mgm. % Drug discontinued.
2.	J.M.	Reddish maculopapular eruption over face, neck, trunk, extremities, especially flexor surfaces. Appeared 7 days after starting, resolved 2 to 3 days after withdrawal.	November 1, 1945, 1.3 mgm. % November 2, 1945, 8.5 mgm. % November 8, 1945, 11.2 mgm. % November 11, 1945, 11.2 mgm. %
3.	M.V.	Maculopapular eruption over back and flexor aspect of forearms. Appeared 4 days after starting loading, disappeared 4 days later.	November 1, 1945, 1.0 mgm. % November 2, 1945, 7.0 mgm. % November 9, 1945, 3.3 mgm. % (3 days after drug stopped.)
4.	G.M.	Severe coryza, 24 hours later. Redness and marked swelling of periorbital area (right) 2 days later. Nausea and vomiting. Subconjunctival hæmorrhage. 1.5 cm. (right) and conjunctival injection (left) on 4th day. Œdema did not disappear after s.c. injection of adrenalin m. v.	November 1, 1945, 0.7 mgm. % November 3, 1945, 8.5 mgm. % November 12, 1945, 5.2 mgm. % (7 days after drug stopped).
5.	C.R.	Occasional reddish papules over feet and legs accompanied by chilblains. Both disappeared 5 days later.	May 7, 1945, 0.6 mgm. % May 8, 1945, 7.6 mgm. % May 14, 1945, 8.0 mgm. %
		3-DAY LOADING	
1.	J.P.	"Coryza" (Asthma since childhood, uses ephedrine inhaler).	November 2, 1945, 0.9 mgm. % November 5, 1945, 7.0 mgm. %
2.	K.J.	Headache—2 days after starting. Drowsiness—7 days after starting. Reddish maculopapular eruption, 0.5. cm. in size, over lumbosacral area (disappeared 3 days after withdrawal).	November 2, 1945, 1.3 mgm. % November 5, 1945, 7.0 mgm. % November 8, 1945, 7.4 mgm. %
3.	M.K.	Nausea, vomiting, diarrhœa during loading period.	November 2, 1945, 0.3 mgm. % Drug discontinued.

is determined at weekly intervals; after a fair degree of stability is achieved, this determination is carried out fortnightly.

The selection of patients.—The proper selection of patients for thiocyanate therapy is of the utmost importance. An unwise choice of patient may prove just as serious an error as improper administration of the drug. Indeed, a number of the toxic reactions reported seem to have occurred in patients to whom the drug, in our opinion, should not have been given.

The prime indication for potassium thiocyanate is for the relief of the severe headaches of the hypertensive patient. In our experience, there is no other agent nearly so effectual in lessening the intensity and frequency of this distressing symptom. Indeed, we would agree with Page and Corcoran[8] that for this symptom, at least, it is "a sovereign remedy". We have also used thiocyanate with complete success in a case of severe migraine unassociated with hypertension, as had been reported earlier by Hines.[9])

Potassium thiocyanate should not be used primarily for its hypotensive properties, which, in our hands, are not impressive. We have seen appreciable reductions of both systolic (up to 60) and diastolic (up to 30 mm. of mercury) pressures in our clinic, but our results are not as good in this respect as have been reported by others.

The untoward reactions which we have encountered in therapeutic administration are given in Table VI. Viewed in retrospect, four of these patients, Nos. 1, 2, 4 and 6 should not have been treated with thiocyanate to obtain a hypotensive effect only. In patients Nos. 3 and 5, the drug was given properly for relief of severe headaches, and these reactions could not have been anticipated.

Undoubtedly, the special field for this drug is in the therapy of the relatively young person, with labile blood pressure (group 1 of Keith and Wagener's classification) and severe hypertensive headaches, usually of migrainous type. Thiocyanate can also offer to some patients in Keith and Wagener's group 2, who have more fixed and higher pressures, and some evidences of vascular strain, a worthwhile postponement of cardio-vascular senescence. Of course, as more extensive arteriosclerosis and calcium deposit occurs in the arteries of patients in the more severe stages of hypertension, less retardation of ageing would naturally be expected, and in practice, we do

TABLE VI.

REACTIONS OBSERVED DURING THERAPEUTIC ADMINISTRATION OF POTASSIUM THIOCYANATE ENSEALS

Initials and age	*Diagnosis*	*Dosage*	*Reactions*	*Serum KSCN*	*Treatment*
Mr. E.L. 68	Essential hypertension with failing adaptation, gr. 2-3 (angina pectoris).	gr. vi o.d. X14.	More numerous attacks of angina.	October 5, 1944, 0.3 mgm. % October 12, 1944, 5.2 mgm. %	Pt. discontinued treatment after first week. Died 6 weeks later.
Mr. C.R. 48	Essential hypertension, diencephalic syndrome, gr. 2.	gr. XXI Stat. (Jan. 20, 1945), then gr. iii OH4 x 3, then gr. iii o.d. After Feb. 15, 1945, gr. vi o.d.	Phlebitis of long saphenous vein (lt.) and venous plexus of lt. labia from Feb. 5 to 24, '45. Emesis on Feb. 20.	January 29, 1945, 1.3 mgm. % February 16, 1945, 6.0 mgm. % March 3, 1945, 7.2 mgm. %	H.W.B. locally. Therapy continued after discharge on Feb. 24, at O.P.D. Condition resolved March 17.
Mrs. C.D. 41	Essential hypertension, gr. 3.	gr. vi o.d.	Apthous stomatitis of tongue, lower gingivum, vermilion margin of lip. Feb. 20 to 23, 1945.	February 16, 1945, 11.5 mgm. % February 22, 1945, 10.5 mgm. %	Carbolic acid and alcohol locally. Placebos substituted for enseals. Condition resolved Feb. 25.
Mrs. N.H. 61	Hypertensive heart disease with congestive heart failure, gr. 3—endogenous obesity, pituitary type.	gr. vi t.i.d. X9 then gr. iii o.d. X3.	Severe pain in lt. hip and knee, Dec. 7. Acute hyperæsthesia of lt. leg for 6 days (osteoporosis), drug fever, 99.4-100.4° for 3 days.	December 4, 1945, 0.5 mgm. % December 5, 1945, 3.4 mgm. % December 6, 1945 11.9 mgm. % December 7, 1945, 18.4 mgm. % December 9, 1945, 12.9 mgm. % December 12, 1945, 6.9 mgm. %	Therapy stopped. Dec. 7. Symptoms subsided 5 days after withdrawal.
Mr. C.S. 58	Hypertensive heart disease with failing adaptation, gr. 3.	gr. vi o.d.	Severe occipital and temporal headache for 2 days commencing Aug. 14. On Aug. 16, temp. 102°, sweating, marked weakness, locomotor instability, nausea, several emeses. (thiocyanaye poisoning).	August 12, 1945, 12.5 mgm. % August 17, 1945, 15.4 mgm. % August 20, 1945, 9.0 mgm. %	Admitted to hospital. Enseals stopped. Phenacetin gr. v and caffeine gr. ii p.r.n. for headache. Asymptomatic except for headaches on discharge Aug. 23.
Mrs. S.E. 71	Generalized arteriosclerosis. Hypertensive heart disease with failure, gr. 3. Coronary thrombosis (old). kyphosis.	gr. vi b.i.d. X9.	Severe retromammary pain dyspnoea at rest, considerable weakness on Oct. 12.	October 7, 1945, 1.0 mgm. % October 10, 1945, 10.5 mgm. %	Drug stopped. Nitroglycerine gr. 1/100. Demerol 2 c.c. IM repeated twice. Oxygen therapy. Pt. died 2 months later.

not use thiocyanate in Keith and Wagener's groups 3 and 4.

We believe that thiocyanate is contraindicated in:

1. Patients over 60. The benign systolic hypertension manifested by most of these patients is usually asymptomatic, unless their physician has indiscreetly allowed them to become alarmed. Since this senile form of hypertension is due chiefly to arteriosclerosis of the aorta and other great arteries, one would expect no appreciable effect from the thiocyanate radicle, which probably acts on the precapillary arteriole. Indeed, any attempt to treat this form of benign senile hypertension with drugs is "meddlesome therapy".[10]

2. Patients with cardiac or cerebral complications. It is only to be expected that if thiocyanate, administered to a patient with angina, does succeed in lowering the blood pressure appreciably, its effects may be the opposite of beneficial. Lowering of the coronary pulse pressure may critically lessen the oxygen supply to the myocardium, and embarrass or seriously endanger the patient.

Whether intimal hæmorrhage that may damage the endothelium and enhance thrombosis, as noted by Paterson,[11, 12] is of the same pathogenesis as the petechiæ or intracutaneous hæmorrhages noted by Griffith[13] in his capillary permeability test remains to be demonstrated. However, the latter has stated that a petechial index of 8 to 13 is a moderate, and of more than 13, a definite contraindication to thiocyanate medication. He believes that thiocyanate increases capillary fragility, although he feels that in some cases rutin[14] may be given orally to repair this damage, thus salvaging these patients for thiocyanate therapy.

Patients with failing renal reserve may commence suddenly to accumulate the thiocyanate, and in a few instances, this has led to severe intoxication and death within a few days.[15] All that can be done in the case of such a toxic pile-up is to withdraw the drug and stimulate glomerular filtration with physiologic saline intravenously. Thiocyanate is rather obviously contraindicated in any patient with myocardial failure, since a further reduction of arterial pulse pressure, and of tissue perfusion (if effected), would only further embarrass an overtaxed organ.

3. Patients with a history of drug intolerance.

4. Patients who cannot have blood estimations performed at regular intervals. This may be due to transportation difficulties, psychological irresponsibility or inaccessibility of superficial veins in obese persons. As already stated, our practice is to make a serum estimation every two weeks, unless the patient's optimum therapeutic level has been established at less than 6 mgm. %, as may sometimes happen. In these cases, we feel that a monthly estimation is safe.

5. No patient with malignant hypertension (and established papillœdema) should be given thiocyanate. We have followed several patients relieved of crippling headaches with thiocyanates, into this phase of their disease, and have felt that the dangers of cumulation of the drug, because of the associated renal failure, were such as to vitiate its use.

SUMMARY

This report presents a method of administering thiocyanate to patients suffering from arterial hypertension with severe headaches. Earlier experiments on "cyanating" patients are detailed and, finally, the details of a practical method of applying and assessing this method of therapy are given.

For the "average" patient of 150 lb., the loading dose is suggested to be 0.8 gm. of potassium thiocyanate 4-hourly for 3 doses. The maintenance dose for the majority of patients is 0.4 gm. daily thereafter.

The indications and contraindications for this method of therapy are discussed.

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